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THE THREAT OF SYNTHETIC SMALLPOX – EUROPEAN PERSPECTIVES

Abstract

This article explores how advances in synthetic biology, and the potential threat of deliberately recreating and spreading smallpox, are affecting the multilateral debate on the remaining variola virus stocks. It draws on in-depth, semi-structured interviews with 10 high-profile, European-based experts in biosecurity and synthetic biology.

Four overarching themes impacting the retention/destruction debate are discussed, relating to biosecurity, dangerous knowledge, accidental releases, and eradication. The article concludes that while synthetic biology seems to affect all the main discourses within the variola stocks debate, a range of views is present and it is not apparent that advances in synthetic biology are causing a shift towards either retention or destruction of the stocks.

The Smallpox Stocks Debate

In December 1979, the World Health Organization (WHO) celebrated one of global health's greatest accomplishments: the eradication of smallpox, one of the most lethal diseases humankind has ever faced. Since then, stocks of the variola virus that causes smallpox have been kept at two WHO Collaborating Centres, one in the USA and one in the Russian Federation. From early on, these stocks were controversial. By 1986, with no new smallpox cases reported, the World Health Assembly—the decision-making body of the WHO—resolved to destroy the strain collections and make the virus extinct. But there was resistance to the idea; in particular, from microbiologists keen to continue medical research on the virus. This resistance has endured, and a final decision on stock retention/destruction has still not been reached.

In the years since stock destruction was first tabled, the science for understanding infectious diseases and inventing defences against them has made significant advances. These trends have led to a diminished need to use live variola virus for research, and have reduced public health needs to retain smallpox stocks (1). But there have also been other scientific advances that impact the debate, most significantly in the field of synthetic biology. In recent years it has become technically possible to recreate the variola virus from scratch: "While recreating variola is quite complex, it is increasingly possible due to the availability of genetic material and of machines for complex assembly, as well as increasing know-how among a broad array of persons. Furthermore, the rapid rise in availability of genetic material from commercial sources and the so-called 'grey market' is driving the cost of this material down, making re-creation possible by multiple institutions and persons, including those with malicious intent" (2). Illustrating the point, a group of Canadian researchers led by virologist David Evans at the University of

Alberta recently claims to have synthesized the extinct horsepox virus, a relative of smallpox, from genetic pieces ordered in the mail for around $100,000 (3). While the aim of the as-yet unpublished experiment performed in 2016 was to "help unravel the origins of a centuries-old smallpox vaccine and lead to new, better vaccines or even cancer therapeutics", it has also been pointed out that the technique Evans used could be used to recreate smallpox (3,4,5). These sorts of scientific developments mean the risk of smallpox re-emerging can never be fully eradicated.

The aim of this article is to explore how advances in synthetic biology, and the potential threat of deliberately recreating and spreading smallpox, are affecting the debate on the remaining variola stocks. The lack of historical data on the deliberate spread of disease means biological threat judgements rest largely on expert opinions (6). To date, much of the expert commentary on the smallpox re-emergence debate, as well as the larger biosecurity debate around synthetic biology, has been dominated by US perspectives. This article reports on a pilot project specifically investigating European expert perspectives to explore how these views may or may not differ from US perspectives. While synthetic biology includes different engineering techniques, the study focuses particularly on those that allow the reconstruction of a virus, achieved for the first time in 2002 by Cello, Paul and Wimmer and their team who reconstructed the polio virus, and shortly thereafter, in 2005, by Tumpey and his team who reconstructed the 1918 influenza virus (7,8). Four overarching themes affecting the retention/destruction debate emerged from the interviews; these relate to biosecurity, dangerous knowledge, accidental releases, and eradication, and will be discussed in turn.

Methods

The project draws on in-depth semi-structured interviews with 10 senior European-based experts in biosecurity and synthetic biology. Participants were recruited on the basis of three inclusion criteria: they had to be based within Europe, have a background in biosecurity and/or synthetic biology (preferably both), and be knowledgeable about the smallpox stocks debate. A snowball sample was constructed. Recruitment was through personal contacts and email. The final sample consisted of 6 experts based in the UK, 2 in Germany, 1 in Denmark, and 1 in Switzerland. 8 experts worked in academia, 1 in a think tank and 1 in the biotech industry. 9 experts were male, 1 was female.

The interviews took place between October and December 2016 via Skype, telephone or face-to-face depending on the participants' preference and logistical issues. The interviews lasted between 30 and 60 minutes. All were audio-recorded and transcribed.

The interviews started with a short introduction from the interviewer aimed at triggering comparison between U.S. and European states' involvement in the WHO smallpox stocks destruction debate. We then asked a series of open-ended questions, allowing space for impromptu questions and discussion. Standard questions covered in all interviews included: How balanced, or representative of different opinions, do you find the reports on smallpox stocks destruction? Is there a 'non-US' perspective? In what way do the new engineering techniques introduced by synthetic biology affect the debate, if at all? What do you think about the idea of *complete* eradication in a world where we have the ability to synthesize a virus in the laboratory? How likely is a 'man-generated' epidemic? How accessible is scientific information on how to re-create a virus? How confident are you that all smallpox samples have been transferred to the two high-security laboratories in the U.S. and Russia? Should this affect 'our' [European] judgment on whether to keep the stocks?

In presenting the interview findings, we have in general sought to present the majority opinion and chosen the best quote to illustrate that view to the reader. However, where interesting and relevant minority opinions were found, they have been included to convey the variation.

Biosecurity

The likelihood of deliberate re-introduction of smallpox formed a core element of the study interviews. While acknowledging that the likelihood of deliberate smallpox re-introduction is ultimately unknown, the interviewed experts assessed the risk to be small, but increasing with advances in synthetic biology—reflecting similar findings from other studies in the field such as that by Gaudioso and colleagues (9).

As part of the risk assessment discussions, the experts also focused on the sorts of actors who might use synthetic biology to deliberately recreate smallpox. Some highlighted the role of non-state actors and noted, for instance, that: *"Traditionally we've said that biological weapons, in particular complicated ones, like variola, could only be produced by state actors. ... In my opinion synthetic biology fundamentally changes the debate. ...threat [assessments hinge on] whether or not a non-state actor could theoretically access this type of weapon. And the answer to that is [now] yes, at least theoretically, they can access it. And, in ten years' time, the argument will probably not even be theoretical anymore."* Similarly, another expert said that with advances in synthetic biology "*the [stock retention/destruction] discourse has to be problematized, unpacked, and expanded to include the non-state actor threat and the impact of synthetic biology.*"

Most experts interviewed, however, focused on state, or state-sponsored, actors. While they agreed synthetic biology may create an 'opportunity' for non-state actors to recreate the virus, they stressed that this does not mean it has become an easy process. They noted that using synthetic biology to recreate viable viruses is still at an early stage, and that scientists are struggling with the various steps involved. It was also emphasised that creating a viable virus is not the same as creating a biological weapon, and that the weaponisation process is long and complicated. The findings echoed those of other studies focusing on European or international perspectives such as Lentzos (2014) and Jefferson and colleagues (2014) (10,11). One expert explained that synthetic biology makes it look like someone could "*simply write a protocol for how to create a super-strength virus*" but, in reality, infrastructure and knowledge are needed in order to follow such protocol and therefore "*the real threat*" still "*comes from large actors and organisations at state level*".

The interviewed experts generally agreed that the scientific research argument for retaining the stocks has largely disappeared, but that any attempts to chemically synthesize whole-scale variola virus would likely give rise to suspicion and alarm at the international level. One expert argued that retaining the physical virus stocks now primarily serves a national security purpose: destroying the stocks "*is always something people and governments are unwilling to do because it is like a nuclear option in that if people think you have the intact virus, it serves as a bit of a deterrent."* So while the retention/destruction debate is often cast as a scientific and technical debate, he argued that it will increasingly become more political and national security focused.

Dangerous Knowledge

Most experts interviewed agreed that synthetic biology has added a new dimension to the politicization of an already highly political debate. Synthetic biology was seen as having linked the retention/destruction debate to broader discussions about oversight of life science advances, and in particular to discussions about the production of dangerous knowledge and the restriction of scientific research.

Focusing on this second theme, i.e. the information available for misuse, the interviewees generally acknowledged that information is available that could be misused, but most were quick to highlight that this information does not come in the form of 'recipes' or 'how-to' manuals—echoing Michael Kenney's work on *techne* (abstract technical knowledge) and *mētis* (practical, experiential knowledge) (12,13,14). One expert said, for instance: *"In my opinion, you do not find a complete recipe which gives all details from step A to Z on how to recreate a virus, especially the smallpox virus. This information is simply not there. But there is enough technical information available which shows you how to accomplish several critical steps on the way to recreating a virus."* Another expert pointed out, for instance, that while the genome sequence of one of the strands of variola major is available online, there is not a publicly available scientific paper that provides a protocol for how to recreate the variola virus from the sequence.

The difficulty of using the information, despite it being available, was echoed by a number of the interviewees. One expert noted that "*the DNA sequences of many viruses are readily available but that doesn't necessarily mean you can make one. And even if you can manufacture one, put the chemical bits together, it doesn't mean it is going to be a live functioning virus, scientists still have problems with that. … And even if you know how to make one it certainly does not mean you are able to make a weapon."* Similarly, another expert pointed to barriers created by a lack of expertise and a "*deep scientific background"* to make sense of most scientific information. And even scientific expertise

is not always enough; scientists often have difficulties replicating each other's experiments: "*There are potentially large obstacles to being able to use information on how to recreate a virus…if you are not the person involved in the original experiment."* Or, as someone else pointed out, *"Just being a biologist is not enough. …you need lots of skills in order to do these experiments.*" Others highlighted the role of infrastructure and the expertise of groups rather than lone individuals.

Despite the general consistency of views on this, it was also noted that just because an experiment is hard "*it doesn't mean it is impossible*", especially considering the rapid advances in technology and life sciences: "*we have possibilities [now that] we did not have 20 years ago*".

Accidental Releases

A third theme that arose related to the retention/destruction debate was concern about accidents, with the majority of experts interviewed believing accidental releases more likely than an intentional release of variola. Many noted how common accidents are, and referenced recent biosafety breaches at high security labs in the US, including labs run by the Centers for Disease Control and Prevention (CDC)—one of the two WHO Collaborating Centres for the smallpox stocks. References were also made to the 30-year old live smallpox virus found in a disused refrigerator at the National Institutes of Health in 2014, and concerns were expressed about other forgotten or mislabelled stocks that could pose a danger. The deliberate retention of stocks in facilities outside of the two official WHO Collaborating Centres was also raised.

Many thought the possibility to synthetically manufacture variola provided clear grounds for eliminating the physical virus stocks: as the virus can be 'brought back' at

any point, the stocks would become irrelevant: "*We simply don't need them anymore*". And getting rid of the stocks was perceived as decreasing the risk of accidental releases. In one expert's judgement: "*For me it is a question of balance and I think, on balance, destroying the stocks would make us slightly safer*."

But some were concerned that labelling the stocks as irrelevant could create additional security concerns around the stocks. Because of their physical location in the US and in the Russian Federation, one expert explained, *"If we went down the path of 'if you destroy, I destroy,' I am not sure the Americans would believe that the Russians have destroyed them just like the Russians would not believe the Americans have. It would create more security concerns than it would help."*

Another concern raised by eliminating the stocks in an age of synthetic biology was that it could create a "*false hope, a false promise, a fantasy of security*", not just because the virus could deliberately be recreated in its entirety, but because it would not be a solution to all the other issues wrapped up in the debate.

Eradication

The final theme relates to eradication. The interviews suggested that the experts interviewed held different understandings of the meaning of eradication. Some considered eradication at the disease level, in terms of '*circulating virus'*, and believed the disease can be eradicated even if there are still some reservoirs of the virus. Others considered eradication at the viral level, where the presence of variola stocks meant '*complete eradication'* was not yet achieved.

In this context, the possibility of re-creating a virus in the laboratory was judged by most experts as a factor affecting the concept of eradication as they understood it.

"With synthetic biology, the idea of eradication has been completely undermined: even if you can eradicate a virus in nature scientists can re-create it in the laboratory. This is just to say that we need to look at how the idea of eradication worked in different contexts and how people still believe in the idea of eradication even though absolute eradication is not possible." Others highlighted that the possibility of re-creating variola synthetically means eradication can no longer be linked with permanence: "*As a consequence of synthetic biology there may not be a permanent eradication, and we must always remain open to the possibility of people recreating it in the future*." However, it was pointed out that the possibility of something happening does not necessarily mean that it will occur, and "*in 400 hundred years' time [we] could look back and still say there has not been a case of smallpox since the late 1970s*".

Conclusion

Analysis of the findings shows a range of opinions on the implications of synthetic biology for the smallpox stocks debate, as well as on the dynamics and wider debates in which it lies. The findings are in line with previous studies on biological threat judgements where substantial diversity of views has also been found among experts (6,10,11).

The variety of opinion on the implications of synthetic biology for the smallpox stocks debate could lead to increased uncertainty in future risk assessments of potential smallpox outbreaks. It could also lead to increased challenges in reaching agreement on appropriate regulation of variola research, and more hesitation at a time when decisive steps need to be taken to manage the risk of a man-made smallpox outbreak.

Although the study was small, and can only be indicative not representative, it suggests that the emphasis of European-based experts' perspectives may differ somewhat from that of their American counterparts. A further, more comprehensive, study would be required to bear this out.

Finally, the study has shown that synthetic biology essentially affects all the main discourses within the smallpox stocks debate: from biosecurity to the meaning of eradication itself. However, advances in synthetic biology do not seem to be causing a shift towards either retention or destruction of smallpox stocks, and arguably gives rise to novel risks and additional questions, thus complicating and extending the eradication debate. As one interviewee put it: *"Synthetic biology has affected the debate on both sides but has not got us anywhere closer to a solution."*

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